ISSN No. 2456-4400
Int J Med Lab Res 2018, 3(2): 7-15

IJMLR International Journal of Medical Laboratory Research

RESEARCH ARTICLE

HEPARIN COFACTOR II AND HAEMATOLOGICAL PARAMETERS AMONG PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA: A SINGLE CENTRE STUDY IN NORTH EAST MALAYSIA

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Received: 29 March, 2018/Revision: 15 May, 2018/ Accepted: 10 June, 2018

ABSTRACT: Background: Obstructive sleep apnoea (OSA) is seen among patients with various health co-morbidities. The reason of this study was to compare the haemostatic and haematological parameters between OSA patients and control group. **Methods:** A cross sectional comparative study was performed at a tertiary centre in Kelantan state of Malaysia. The diagnosis of OSA in all patients was confirmed by polysomnography. Laboratory parameters investigated were prothrombin time (PT), activated partial thromboplastin time (APTT), heparin cofactor (HC) II, activated protein C resistance (APC-R), von Willebrand factor (vWF) antigen, factor VIII assays, haemoglobin (Hb), haematocrit (Hct) and platelet count.. **Result:** A total of 14 male OSA patients and one female (n=15) with nearly age-matched 19 healthy individuals (female n=4) were recruited during seven months study period. All of them except one were overweight or obese and a few of them had other medical co-morbidities. Majority of them were already on definitive treatment for OSA. There were statistically significant mean differences in the levels of Hb, Hct, platelet count and HCII in the study group as compared with the control subjects.A low natural HCII among OSA group was recorded. These changes might render them at potential risk of chronic hypercoagulable state. **Conclusions:** Definitive risk of haemostatic abnormalities and outcomes of OSA patients with various medical co-morbidities should be further investigated. As OSA is an emerging disease in various developing countries, the long term related complications should be explored especially on transient or persistent haemostatic changes following treatment.

KEYWORDS: coagulation tests, medical co-morbidities, Heparin Cofactor II, hypercoagulable state, sleep apnoea.

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INTRODUCTION:

Obstructive sleep apnoea (OSA) is a common type of sleep disorder characterized by recurrent episodes of apnoea and hypopnoea due to obstruction of the upper airways when the patient is asleep. The incidence of OSA is increasing in trend especially in development countries related to sedentary lifestyles as well as increasing age in the general population. Untreated OSA has been recognized as an independent risk factor for various co-morbidities(including ischaemic heart disease, cerebrovascular accidents and hypertension)and mortalities[1,2]. The pathogenesis isthought to be related to endothelial dysfunction during the apnoeic episodes that leads to a hypercoagulable state[3]. Previous studies found that Hct, blood viscosity,certain clotting factors (FXIIa, FVIIa and thrombin), platelet activity and whole blood coagulability are increased in patients with OSA. These findings suggest that OSA is associated with a procoagulant state[4].Natural anticoagulants play a major role in haemostasis. Enhanced activity of procoagulant factors may cause haemostatic imbalance leading to a prothrombotic state that resembles deficiencies of natural anticoagulants[5]. Protein C is an important natural anticoagulant, together with protein S, serves in the inactivation process of factors V and VIII. Factor V Leiden mutation, a genetically determined activated Protein C resistance (APC-R) state, has been linked to increased risk of thromboembolism (TE)[6].Interestingly, an acquired form of APC-R state,also can be measured by standard coagulation APC-R assay has been reported and associated with inflammation, vascular, or connective tissue disorders[6]. Procoagulant factors such as factor VIII and vWF may also be involved in OSA which is related to the hypercoagulable state. Raised factor VIII is seen in endothelial dysfunction and chronic systemic inflammation. High factor VIII could contribute to the APC-R state as a result ofimbalance between anticoagulant activity of protein C and clotting factors[7]. There is considerable enough data that relateshypercoagulable and OSA[4,8],but limited reports on OSA patients with concurrent medical co-morbidities and its effect on the natural anticoagulant system. Alongitudinal population-based cohort study showed that patients with OSA even without diabetes or hypertension are at higher risk of developing chronic kidney disease (CKD) over the next 3 years and nearly 2.5 months earlier than the non-OSA cohort[9]. For a reliable assessment of the haemostatic effect of OSA, it is important to select patients at the time before treatment and compare the findings after treatment completed. However this approach is quite difficult due to the chronicity of concurrent medical problems that co-existed in OSA patients which can influence the haemostatic activity and other laboratory parameters. Hence this study did not exclude OSA patients with underlying medical co-morbidities. This is a descriptive study on haemostatic changes among confirmed OSA patients with and without medical co-morbidities and compared with the healthy control group. Overweight or obesity is considered as a co-morbid state together with other medical conditions.

It may be clinically useful to know whether patients with OSAhave abnormal natural anticoagulant activity indicating impairment of the haemostatic function. Hence, this study was carried out to investigate on the specific natural anticoagulant properties [heparin cofactor II (HCII) and APC-R] as well as other selected parameters that may be associated with abnormal haemostatic changes in OSA patients.

MATERIALS AND METHODS:

Subjects

A comparative cross sectional study was conducted at Hospital Universiti Sains Malaysia (USM) located at North East region of Peninsular Malaysia for a period of seven months. A total of

15 OSA patients and 19 healthy adult volunteers with normal body mass index (BMI)ie control subjects were recruited for this study. Ethical approval for this study was obtained from The Human Research Ethics Committee, USM. (FWA Reg. No 00007718, IRB Reg No: 00004494).

The OSA patients included in this study had been under active follow up at Otorhinolaryngology (ORL) clinic, HUSM and had undergone complete clinical assessment for establishing OSA diagnosis. Complementary clinical information was obtained from patients' medical records and the treating doctors. Such data included the demographic information,medical co-morbidities includingbody mass index (BMI) of patients and the methods of treatment of OSA. The participants were diagnosed with OSA with an overnight polysomnography and were classified according to their Apnoea-Hypopnoea Index (AHI) scores and were categorized as: Normal: 0-4; Mild: 5-14; Moderate: 15-29 and Severe: 30 or more. These scores were measured by the number of apnoea and hypopnoea episodes per hour of sleep. One episode of apnoea must last for at least 10 seconds and be associated with a decrease in blood oxygenation documented at the sleep laboratory. Combining AHI and oxygen desaturation gave an overall sleep apnoea severity score which evaluated both the number of sleep disruptions and degree of oxygen desaturation (low oxygen blood level)[1,2].

The control subjects of this study were almost age matched, healthy, having normal body weight with no past medical co-morbidities. Patients who were below 13 years of age, on antithrombotic therapy, on contraceptive pills, having underlying congenital haemostatic disorders, thrombocytopaenia, chronic coagulopathies or chronic liver disease were excluded. In addition, patients who had a recent history of myocardial infarction (MI) or stroke during the preceding 3 months were also excluded.These criteria ensured the laboratory findings of the OSApatients were not influenced by haemostatic changes related to recent onset of MI/stroke or drug effect that could alter the coagulation parameters.

Study procedures

Blood samples were collected from each study subject with minimal stasis. From each study subject, 10 mls of blood was withdrawn and put in three sodium citrate containers and one ethylene diamine tetra acetic acid (EDTA) container for the haemostatic study and haematological parameters respectively. All laboratory investigations were performed at the Haematology Laboratory, Hospital USM and included Hb, Hct, platelet count, PT and APTT, HC II level, APC-R, FVIII and vWF assays. For coagulation studies, the citrated blood was prepared by double centrifugation at1500g for 15 minutes to obtain the platelet poor plasma (PPP). The PPP was transferred into three separate bullet containers using a polypropylene transfer pipette. All aliquoted plasma samples were stored at -80°C until further analysis. For analysis, the plasma samples were thawed down in a water bath at 37°C for 5 minutes. The blood collection, processing and storage were performed according to the Clinical Lab Standardization Institute (CLSI) guidelines for coagulation tests. Measurements for Hb, Hct and platelet counts were performed using the Sysmex XE 5000 analyzer (Sysmex, Kobe, Japan) as in the manufacturer's instructions.

The STA®- Neoplastine ® CI plus and STA-APTT Automate were used in this study for the determination of the PT and APTT in plasma using STA-R evolution (Diagnostica Stago, Asnières, France). The FVIII assay was performed with IL reagent using ACL Elitepro Instrumentation (Elitepro Instrumentation Laboratory, Milan, Italy).The test was performed for quantitative determinations of FVIII activity in citrated plasma based on the APTT assay. Each patient's plasma was diluted and added to plasma deficient in FVIII. Correction of the clotting time

of the deficient plasma is proportional to the concentration (% activity) of that factor in the patient plasma which was interpolated from a calibration curve.

The vWF antigen assay was performed using ACL Elitepro Instrumentation (Elitepro Instrumentation Laboratory, Milan, Italy). The assay is an automated latex particle enhanced turbidimetric immunoassay for the quantitative determination of vWF antigen in plasma. The degree of agglutination is directly proportional to the concentration of vWF antigen in the sample and is determined by measuring the decrease of transmitted light caused by the aggregates.

The test for HCII was performed using the STA-COMPACT(Diagnostica Stago, Asnières, France). This assay utilized the colorimetric method for HCII. The method was adapted from Manufacturer's instruction (Diagnostica STAGO).

The assay for APC-R was performed using STACLOT® APC-R with the STA-COMPACT analyser (Diagnostica STAGO,Asnières France). The assay utilizes the clot based assay method for the assessment of APC-R in the citrated human plasma, sensitive to factor V Leiden mutation. The method was also adapted from the manufacturer's catalogue. The results were expressed in seconds. There was a variation of results indicating various degrees of activated protein C activity.The cut off time above 120 seconds indicated a normal assay and not clinically significant to suspect APC-R state. The cut off level was validated prior to sample testing.

All data was analyzed using the Statistical Package or Social Sciences (SPSS) software version 19. Demographic data was determined with frequencies statistics. Mean values were determined for thestudied parameters for parametric results. The difference of mean between the two groups was analyzed using the independent t- test for parametric assays.

RESULTS:

A total of 15 OSA patients (all males except one) and 19 healthy adults (15 males and 4 females)were recruited during the study period. The age range of the study patients was 20 to 69 years with a mean age of 43 years. The age range of the control subjects was 20 to 59 years with a mean age of 35 years. Polysomnography of the studied patients showed that 80% (n= 12) of the patients suffered from severe sleep apnoea, with AHI≥ 30, and the other 20% of patients had moderate/intermediate AHI of 15-29.

Continuous positive airway pressure (CPAP) therapy was the main treatment done in 10 of them (67%), surgical intervention was done in 2 of them (13%). The remaining patients were waiting for the definitive therapy at the time of this study was conducted. Of all the subjects, 5 hadhypertension, hypertension with diabetes mellitus, hypertension with ischaemic heart disease, hypercholesterolaemia and epilepsy were recorded, in each of them respectively (n=5). The BMI of all the control subjects was within the normal range between 18.5 – 22.9. The BMI of the studied subjects was more than 23 except 1 patient, indicatingthat 93% of the patients were overweight or in the obese category. The mean Hb of OSA patients and the control group were 15.5 (±1.0) and 13.9 (±1.2) g/dl, respectively and this difference was statistically significant ($p<0.001$). The Hct mean values also showed a significant difference between OSA and control subjects [patients Hct mean was 44.7% (±2.2), control 41.9% (±2.5), and p= 0.004]. The mean platelet countin the OSA subjects was noticeably lower than that of the control group [228.3 (±78.5) and 287.3 (±63.1)($x10^9$/l), respectively, p= 0.021]. The mean PT in the OSA patients group was not significantly different than in the control subjects (p=0.399). The remaining parameters tested for APTT, FVIII assay and vWF antigen also did not show significant mean differences between OSA patients and the control subjects.

Comparison of the mean APC-R of the OSA patients and the control subjects also showed no statistically significant difference with 166.83 (±19.26) seconds in the OSA patients and 160.37(±31.27) seconds in the control subjects.

There was a significant difference in the mean of HCII level of the OSA group as compared to that of the control subjects. The mean HCII was 90.87± 14.13% in the OSA group and 115.14± 25.65% in the control subjects (p=0.004). There was also a significant difference for HCII between severe and moderate OSA patients based on AHI [100.3 (±10.60) and 88.50 (±14.25) respectively, with a p-value of 0.011].The severe OSA patients showed the lowest mean value. All of the results were summarized in Table 1.

Table 1: Comparison of various haematological and haemostatic parameters among OSA patients and control subjects

Variables	Control	OSA patients	Mean difference	p-value*
	(n=19)	(n=15) (95% CI)		
	Mean (SD)	Mean (SD)		
Hb (g/dl)	13.9(1.2)	15.5(1.0)	-1.6(-2.4, -0.8)	**<0.001**
Hct(%)	41.9(2.5)	44.7(2.2)	-2.7(-4.5, -0.9)	**0.004**
Platelet ($x10^9$/l)	287.3(63.1)	228.3(78.5)	58.9(9.5, 108.4)	**0.021**
PT(secs)	12.7 (0.6)	12.8 (0.3)	-0.1 (-0.5, -0.2)	0.399
APTT(secs)	39.3(2.4)	38.0(4.2)	1.3(-1.1, 1.3)	0.285
FVIII assay (%)	99.9(35.2)	120.8(111.6) -20.9(-76.1, 34.3)	0.446	
vWF antigen(%)	101.5(29.5)	84.3(29.3)	17.3(-3.4, 37.9)	0.099
HCII (%)	115.14(25.65)	90.87(14.13)	24.27(8.64, 39.30)	**0.004**
APCR (secs)	160.37(31.27)	166.83 (19.26)	-12.61(-38.34, 13.10)	0.325

* Independent t-Test, significant p value is <0.05

DISCUSSION:

The OSA syndrome is recognized as a sleep disorder that commonly affects the population and has been strongly associated with multiple medical co-morbidities, hypercoagulable state, cardiovascular related mortality as well as impaired quality of life[10]. The hypercoagulable state is associated with acquired and inherited causes. Among inherited hypercoagulable conditions are Factor V Leiden, Prothrombin gene mutation and deficiencies of natural anticoagulants including antithrombin, protein C and protein S. Acquired hypercoagulable conditions include cancer, obesity, pregnancy, oestrogen therapy, antiphospholipid antibody syndrome and nephrotic syndrome[11].

The findings of the current study agreed with most of the previously reported studies regarding OSA, including the age of patients and the severity of their conditions, and mode of treatment[12,13].The reported age differences in some of the studies probably depend on the awareness of OSA diagnosis, associated medical co-morbidities and development of complications which may vary from one community to another.

Similarly, the elevations in most of the haematological parameters tested were found to agree with those reported in previous studies, including Hb, and Hct[14]. These alterations could contribute to haemostatic changes, as hypoxia would lead to elevated Hb and Hct, which in turn may increase the blood viscosity and thus may contribute to the hypercoagulability. Hence, increased cardiovascular morbidity and mortality would be partly due to extra burden on the cardiovascular system affecting the endothelial function associated with a blunted response towards nitrous oxide,resulting in reduced vasodilatation and thus elevated blood pressure[15,16].

All the patients had normal platelet count. The reason for reduced mean platelet count among OSA group compared to normal groupis uncertain. This might have been due to the hypoxia, similarly seen at high altitude changes that exert adverse effects on platelet functions and counts with increased tendency for platelets aggregation[17]. Prolonged hypoxia was reported to activate platelet activity but lower platelet count due to chronic consumption requires further

investigation. Hence, increased platelet aggregation among OSA patients may, in turn, increase the risk towards cardiovascular mortality[18].Further studies to confirm the consistent association between hypoxia and low platelet counts and the exact mechanism (s) underlying this hypoxic effect is needed.

In the current study there has been a focus on the risk of hypercoagulable state due to reduced HCII levels among OSA group with or without medical co-morbidities compared to those of the control subjects.Its association with the severity of OSA can be speculated, leading to increased risks of cardiac events. In previous clinical studies, adequate levels of HCII (>80%) have been found to be protective against re-stenosis after angioplasty in coronary artery disease[19] and higher HCII (>122%) may also contribute to lowering all major adverse cardiovascular events as compared to patients with low HCII group (HCII <98%)[20].The lower mean value of HCII in the study group may be due to the effect of OSA, coexisting co-morbidities or both.

The APC-R assay cut-off value for this study was taken as 120 seconds, and above this value it appears to have no significant clinical effect in the protein C anticoagulation system. All OSA patients and control subjects showed results above this cut-off value, and hence not suggestive of having APC-R state. A number of disorders were reportedto be associated with acquired APC-R state, rendering them to develop a hypercoagulability such as lupus nephritis, multiple myeloma, haematological malignancies and chemotherapeutic effect[21]. There was no significant difference between the study groups, and the reason could be attributable to the low incidence of APC-R state from Factor V Leiden mutation in this study population[7]. In addition, the contribution of high factor VIII to the impaired APC function was not shown in this study (see below).

The PT in OSA patients was not significantly different from the control subjects. Shortened APTT was reported in both arterial and venous thrombosis and proved to be related to a hypercoagulable state[7]. Further studies are required to confirm the significance of shortened PT test pertaining to its usefulness and sensitivity in certain conditions of hypercoagulability. However PT is known to be shortened from cold activation process of FVIII during storage and may lead to spurious result from pre-analytical error.

It has already been established that increased FVIII levels is associated with thrombotic events[22]. However, in the current study, there was no statistically significant difference of the FVIII levels and von Willebrand factor between OSA patients and the control group. Moreover, most of the study subjects were receiving treatment at the time of blood taking which might have influenced these findings. It would probably be rewarding to conduct a cohort study to look at the differences in the laboratory parameters before and after OSA therapy. It was reported that the levels of factor VIII in arterial thrombosis and venous thrombosis were elevated to more than 123% and 150%, respectively[23].In fact, 20% of the OSA patients in this study had FVIII levels of more than 150%. vWF antigen is a marker of endothelial dysfunction associated with arterial thrombotic disorder and its complications. While vWF was reported to be increased among OSA patients,this studyand in the other related study showed that its level was not statistically significant in OSA group[4].

The findings of this study could be a platform to more exploratory steps towards understanding the pathophysiological effect of OSA with and without medical co-morbidity. Nevertheless limitations of this study were recognized, especially from the view of descriptive findings and small sample size.

A comparative study among OSA patients using baseline haematological and haemostatic parameters at the diagnosis before treatment and after treatment should be more appropriate. As

discussed before, some of the chronic conditions, ie overweight and obesity are difficult to be excluded among the OSA patients and hence the bias of this issue could not be eliminated by pre and post treatment evaluation per-se. The other limitation was that most subjects with co-morbidities received different types of treatment according to their medical problem.

The findings in this study however showed significant differences in some parameters between the OSA patients and the control subjects, and interestingly they were all having one or more co-morbidities, at least overweight or obese. Although direct association of these parameters were inconclusive, they might, altogether indicate possible unfavorable changes towards developing hypercoagulable events. In this study, the most significant change in the severe OSA patients could be the lowered mean level of HCII which is a direct *in vivo*thrombin inhibitor, suggesting the predisposition towardsa hypercoagulable state. Although the finding could be challenged due to factors other than OSA, the result is important for the management of OSA patients in the presence or absence of the medical problems.

One study reported that CPAP therapy did not prevent cardiovascular events in patients with moderate to severe OSA[25]. Thus the role of laboratory parameters in predicting the development of complications in OSA patients should be explored in a well designed study in future.Moreover this type of study could encourage precision medicine practice using the risk assessment for individual patient management[26].

The role of haemostatic parametersas biomarkers in the disease process and in monitoring OSA patientsshould be explored. A cohort-type study is recommended to be done among newly diagnosed OSA patients and investigate separately between those with and without medical co-morbidities. All laboratory parameters should be repeated and analysed after a definitive treatment for OSA is completed. These approaches could alleviate all the factors thatmight have contributed to the bias of laboratory results from various factors.

CONCLUSIONS:

In this study, haematological and haemostatic parameters alterations were shownin a cohort of OSA patients with high BMI in the majority of them. Therefore these changes could be associated with higher risk of hypercoagulable state in the presence of increased Hb, Hct and lower HCII levels. These changes might be directly or indirectly related to the chronic hypoxia, overweight/obesity and other underlying medical co-morbidities among them.

ACKNOWLEDGEMENTS:

Acknowledgments are due to Professor Dr.Fawwaz Al-Joudi for his unlimited guidance, Mr. Mohd Ashraf and Mr. Khairul Putra for their technical assistance. The authors are also thankful to USM for providing a short term grant numbered 304/PPSP/1312114 to conduct this study.

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CONFLICT OF INTEREST: Authors declared no conflict of interest

SOURCE OF FINANCIAL SUPPORT: Nil

Cite of article: Norasyikin MA, Suhair AA, Marini R, Baharudin A, Zaidah WA. Heparin cofactor II and haematological parameters among patients with obstructive sleep apnoea: a single-centre study in north-east Malaysia. Int J Med Lab Res. 2018;3(2):7–15. http://doi.org/10.35503/IJMLR.2018.0202